FORM PTO-1390 (REV 10-95) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER: MERCK 2397

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. §371

U.S. APPLICATION NO. (If known, see 37 CFR §1.5): 10/088023

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP00/08258	24 AUGUST 2000	14 SEPTEMBER 1999

TITLE OF INVENTION: USE OF THIENOPYRIMIDINES

APPLICANT(S) FOR DO/EO/US: JONAS, Rochus, et al

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ■ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. §371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. §371.
3. ☐ This express request to begin national examination procedures (35 U.S.C. §371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. §371(b) and PCT Articles 22 and 39(1).
4. ■ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ■ A copy of the International Application as filed (35 U.S.C. §371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ■ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ■ A translation of the International Application into English (35 U.S.C. §371(c)(2)).
7. ■ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. §371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ■ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. §371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. §371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. §371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 C.F.R. §§1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 C.F.R. §§3.28 and 3.31 is included.
13. ☐ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☐ Other items or information:

U.S. APPLICATION NO. (if known, see 37 CFR §1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
10/088023	PCT/EP00/08258	24 AUGUST 2000

17. ☒ The following fees are submitted:

BASIC NATIONAL FEE (37 CFR §1.492 (a) (1) - (5)):

		CALCULATIONS PTO USE ONLY
Search Report has been prepared by the EPO or JPO	$890.00	
International preliminary examination fee paid to USPTO (37 CFR §1.482)	$710.00	
No international preliminary examination fee paid to USPTO (37 CFR §1.482) but international search fee paid to USPTO (37 CFR §1.445(a)(2))	$740.00	
Neither international preliminary examination fee (37 CFR §1.482) nor international search fee (37 CFR §1.445(a)(2)) paid to USPTO	$1040.00	
International preliminary examination fee paid to USPTO (37 CFR §1.482) and all claims satisfied provisions of PCT Article 33(2)-(4)	$100.00	

ENTER APPROPRIATE BASIC FEE AMOUNT =	$890.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 C.F.R. §1.492(e)).		

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	2 - 20 =	0	x $ 18.00	$0.00	
Independent claims	1 - 3 =	0	x $ 84.00	$0.00	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $ 280.00		
TOTAL OF ABOVE CALCULATIONS =				$890.00	
Reduction of 1/2 for filing by small entity, if applicable. A Verified Small Entity Statement must also be					
SUBTOTAL =				$890.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 C.F.R. §1.492(f)).					
TOTAL NATIONAL FEE =				$890.00	
Fee for recording the enclosed assignment (37 C.F.R. §1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 C.F.R. §§3.28, 3.31). $40.00 per property.					
TOTAL FEES ENCLOSED =				$890.00	
				Amount to be refunded:	
				charged:	

a. ■ A check in the amount of $890.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. 13-3402 in the amount of $ _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ■ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 13-3402. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 C.F.R. §§1.494 or 1.495 has not been met, a petition to revive (37 C.F.R. §1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO: Customer Number 23,599

23599
PATENT TRADEMARK OFFICE

Filed: 14 MARCH 2002
AJZ:kmo

SIGNATURE

Anthony J. Zelano
NAME

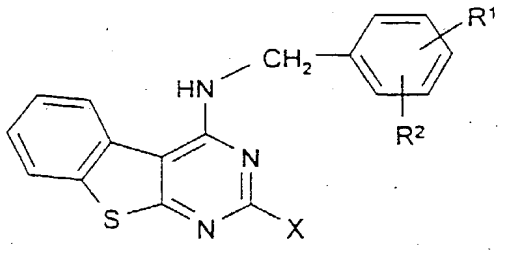
27,969
REGISTRATION NUMBER

Merck Patent Gesellschaft
mit beschränkter Haftung
64271 Darmstadt

Use of thienopyrimidines

Use of thienopyrimidines

The invention relates to the use of compounds of the formula I



I

in which

R^1, R^2 in each case independently of one another are H, A, OA, OH or Hal,

R^1 and R^2 together are also alkylene of 3-5 carbon atoms, $-O-CH_2-CH_2-$, $-CH_2-O-CH_2-$, $-O-CH_2-O-$ or $-O-CH_2-CH_2-O-$,

X is R^4, R^5 or R^6, monosubstituted by R^7,

R^4 is linear or branched alkylene of 1-10 carbon atoms, in which one or two CH_2 groups may have been replaced by -CH=CH- groups,

R^5 is cycloalkyl or cycloalkylalkylene of 5-12 carbon atoms,

R^6 is phenyl or phenylmethyl,

R^7 is COOH, COOA, $CONH_2$, CONHA, $CON(A)_2$ or CN,

A is alkyl of 1 to 6 carbon atoms and

Hal is F, Cl, Br or I

and their physiologically acceptable salts and/or solvates for preparing a medicament for treating angina, high blood pressure, high pulmonary pressure, congestive heart failure, atherosclerosis, conditions of reduced circulation through the cardiac vessels, peripheral vascular diseases, stroke, bronchitis, allergic asthma, chronic asthma, allergic rhinitis, glaucoma, irritable bowel syndrome, tumours, renal insufficiency and cirrhosis of the liver and for treating female impotence.

The use of other PDE V inhibitors is described, for example in WO 94/28902.
Pyrimidine derivatives are known, for example, from DE 19819023, EP 201 188 or WO 93/06104.

The invention was based on the object of discovering new compounds having valuable properties, especially those which may be used to prepare medicaments.

It has been found that the compounds of the formula I and their salts combine very valuable pharmacological properties with good tolerability.

In particular, they exhibit specific inhibition of cGMP phosphodiesterase (PDE V).

Quinazolines having cGMP phosphodiesterase inhibitor activity are described, for example, in J. Med. Chem. 36, 3765 (1993) and ibid. 37, 2106 (1994).

The biological activity of the compounds of the formula I may be determined by methods such as are described, for example, in WO 93/06104 or in WO 94/28902.
The affinity of the compounds of the invention for cGMP and cAMP phosphodiesterase is measured by determining their IC_{50} values (the concentration of inhibitor required to achieve 50% inhibition of the enzyme activity).

The measurements may be made using enzymes isolated by known methods (e.g. W.J. Thompson et al., Biochem. 1971, 10, 311). The experiments may be conducted using a modified "batch" method of W.J. Thompson and M.M. Appleman (Biochem. 1979, 18, 5228).

The use of substituted pyrazolopyrimidinones for treating female impotence is described, for example, in WO 94/28902.

The compounds are effective as inhibitors of phenylephrine-induced contractions in cavernous-body preparations of hares. This biological activity may be demonstrated, for example, by the method described by F. Holmquist et al. in J. Urol., 150, 1310-1315 (1993). The inhibition of the contraction shows the activity of the compounds of the invention for the therapy and/or treatment of impaired potency.

The invention provides for the use of the compounds of formula I and their physiologically acceptable salts and/or solvates for preparing a medicament for treating angina, high blood pressure, high pulmonary pressure, congestive heart failure, atherosclerosis, conditions of reduced circulation through the cardiac vessels, peripheral vascular diseases, stroke, bronchitis, allergic asthma, chronic asthma, allergic rhinitis, glaucoma, irritable bowel syndrome, tumours, renal insufficiency and cirrhosis of the liver and for treating female impotence.

The compounds of the formula I may be used as medicament active principles in human and veterinary medicine. Furthermore, they may be used as intermediates for preparing further medicament active principles.

Above and below, the radicals R^1, R^2, R^3, R^4, R^5, R^6, R^7, X and L have the definitions stated for the formulae I, II and III unless expressly stated otherwise.

A is alkyl of 1-6 carbon atoms.
In the above formulae, alkyl is preferably unbranched and has 1, 2, 3, 4, 5 or 6 carbon atoms and is preferably methyl, ethyl or propyl, further preferably isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, but also n-pentyl, neopentyl, isopentyl or hexyl.

X is a radical R^4, R^5 or R^6 that is monosubstituted by R^7.

R^4 is a linear or branched alkylene radical of 1-10 carbon atoms, the alkylene radical being preferably, for example, methylene, ethylene, propylene, isopropylene, butylene, isobutylene, sec-butylene, pentylene, 1-, 2- or 3-methylbutylene, 1,1-, 1,2- or 2,2-dimethylpropylene, 1-ethylpropylene, hexylene, 1-, 2-, 3- or 4-methylpentylene, 1,1-, 1,2-, 1,3-, 2,2-, 2,3- or 3,3-dimethylbutylene, 1- or 2-ethylbutylene, 1-ethyl-1-methylpropylene, 1-ethyl-2-methylpropylene, 1,1,2- or 1,2,2-trimethylpropylene, linear or branched heptylene, octylene, nonylene or decylene. R^5 is also, for example, but-2-enylene or hex-3-enylene. Very particular preference is given to ethylene, propylene or butylene.

R^5 is cycloalkylalkylene of 5-12 carbon atoms, preferably for example cyclopentylmethylene, cyclohexylmethylene, cyclohexylethylene, cyclohexylpropylene or cyclohexylbutylene.
R^5 is also cycloalkyl of preferably 5-7 carbon atoms. Cycloalkyl is, for example, cyclopentyl, cyclohexyl or cycloheptyl.

Hal is preferably F, Cl or Br, but also I.

The radicals R^1 and R^2 may be identical or different and are preferably in position 3 or 4 of the phenyl ring. They are, for example, in each case independently of one another H, alkyl, F, Cl, Br or I or together are alkylene, such as propylene, butylene or pentylene, for example, and also ethyleneoxy, methylenedioxy or ethylenedioxy. Preferably, they are in each case also alkoxy, such as methoxy, ethoxy or propoxy, for example, and also hydroxyl.

The radical R^7 is preferably for example COOH, $COOCH_3$, $COOC_2H_5$, $CONH_2$, $CON(CH_3)_2$, $CONHCH_3$ or CN.

For the entire invention it is the case that all radicals which occur more than once may be identical or different, i.e. are independent of one another.

Accordingly, the invention provides in particular for the use of those compounds of the formula I in which at least one of the specified radicals has one of the preferred definitions stated above. Some preferred groups of compounds may be expressed by the following subformulae Ia to Id, which correspond to the formula I and in which the radicals not designated in any greater detail have the definition stated for the formula I, but in which

in Ia	X	is COOH-, COOA-, $CONH_2$-, $CONA_2$-, CONHA- or CN-substituted R^4, phenyl or phenylmethyl;
in Ib	R^1 and R^2	together are alkylene of 3-5 carbon atoms, $-O-CH_2-CH_2-$, $-O-CH_2-O-$ or $-O-CH_2-CH_2-O-$,
	X	is COOH-, COOA-, $CONH_2$-, $CONA_2$-, CONHA- or CN-substituted R^4, phenyl or phenylmethyl;
in Ic		

	R^1, R^2	in each case independently of one another are H, A, OA or Hal,
	R^1 and R^2	0together are alkylene of 3-5 carbon atoms, $-O-CH_2-CH_2-$, $-O-CH_2-O-$ or $-O-CH_2-CH_2-O-$,
	X	is COOH-, COOA-, $CONH_2$-, $CONA_2$-, CONHA- or CN-substituted R^4, phenyl or phenylmethyl;
in Id	R^1, R^2	in each case independently of one another are H, A, OA or Hal,
	R^1 and R^2	together are also alkylene of 3-5 carbon atoms, $-O-CH_2-CH_2-$, $-O-CH_2-O-$ or $-O-CH_2-CH_2-O-$,
	X	is alkylene of 2-5 carbon atoms monosubstituted by R^7, or is cyclohexyl, phenyl or phenylmethyl,
	R^7	is COOH or COOA,
	A	is alkyl of 1 to 6 carbon atoms,
	Hal	is F, Cl, Br or I.

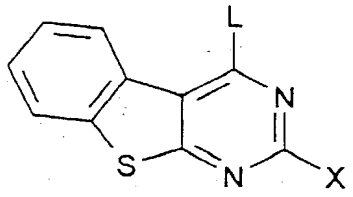
The compounds of the formula I and also the starting substances for preparing them are otherwise prepared by methods which are known per se as are described in the literature (e.g. in standard works such as Houben-Weyl, Methoden der organischen Chemie [Methods of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart), i.e. under reaction conditions which are known and suitable for the stated reactions. Use may also be made of variants which are known per se and are not mentioned in any greater detail here.

In the compounds of the formulae II or III, R^1, R^2, R^3, R^4, X and n have the stated definitions, especially the stated preferred definitions.

If L is a reactive esterified OH group, it is preferably alkylsulfonyloxy of 1-6 carbon atoms (preferably methylsulfonyloxy) or arylsulfonyloxy of 6-

10 carbon atoms (preferably phenyl- or p-tolylsulfonyloxy, and also 2-naphthalenesulfonyloxy).

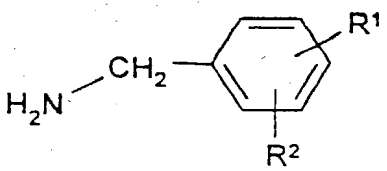
The compounds of the formula I may preferably be obtained by reacting compounds of the formula II



II

in which
X is as defined above
and L is Cl, Br, OH, SCH_3 or a reactive esterified OH group

with compounds of the formula III



III

in which
R^1 and R^2 are as defined above.

The starting substances may also if desired be formed in situ, so that they are not isolated from the reaction mixture but instead are reacted further immediately to the compounds of the formula I.
Alternatively, it is possible to carry out the reaction in stages.

Generally, the starting compounds of the formulae II and III are known. Where they are unknown, they may be prepared by methods which are known per se.

Compounds of the formula II may be obtained, for example, by reaction with $POCl_3$ from the corresponding hydroxypyrimidines, which are synthesized from thiophene derivatives and CN-substituted alkylene carboxylic esters (Eur. J. Med. Chem. 23, 453 (1988)). The hydroxypyrimidines are prepared either by dehydrogenating corresponding tetrahydrobenzothieno-pyrimidine compounds or by the cyclization, customary for preparing pyrimidine derivatives, of 2-aminobenzothiophene-3-carboxylic acid derivatives with aldehydes or nitriles (e.g. Houben Weyl E9b/2).

Specifically, the reaction of the compounds of the formula II with the compounds of the formula III takes place in the presence or absence of an inert solvent at temperatures between about -20 and about 150°, preferably between 20 to 100°.

The addition of an acid-binding agent, for example of an alkali metal or alkaline earth metal hydroxide, carbonate or bicarbonate or of another salt of a weak acid of the alkali metals or alkaline earth metals, preferably of potassium, sodium or calcium, or the addition of an organic base such as triethylamine, dimethylamine, pyridine or quinoline or of an excess of the amine component, may be favourable.

Examples of suitable inert solvents are hydrocarbons, such as hexane, petroleum ether, benzene, toluene or xylene; chlorinated hydrocarbons such as trichloro-ethylene, 1,2-dichloroethane, carbon tetrachloride, chloroform or dichloromethane; alcohols such as methanol, ethanol, isopropanol, n-propanol, n-butanol or tert-butanol; ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran (THF) or dioxane; glycol ether such as ethylene glycol monomethyl or monoethyl ether (methyl glycol or ethyl glycol), ethylene glycol dimethyl ether (diglyme); ketones such as acetone or butanone; amides such as acetamide,

dimethylacetamide, N-methylpyrrolidone or dimethylformamide (DMF); nitriles such as acetonitrile; sulfoxides such as dimethyl sulfoxide (DMSO); nitro compounds such as nitromethane or nitrobenzene; esters such as ethyl acetate, or mixtures of the said solvents.

It is also possible to convert one radical X in a compound of the formula I to another radical X, for example by hydrolysing an ester or a cyano group to a COOH group.

Ester groups may be hydrolysed, for example, with NaOH or KOH in water, water-THF or water-dioxane at temperatures between 0 and 100°.

Carboxylic acids may be converted to the corresponding carbonyl chlorides, for example using thionyl chloride, and these chlorides may in turn be converted to carboxamides. From these carboxamides, carbonitriles are obtained in a known manner by elimination of water.

An acid of the formula I may be converted to the associated acid addition salt using a base, for example by reacting equivalent amounts of the acid and the base in an inert solvent such as ethanol, followed by evaporative concentration. Particularly suitable bases for this reaction are those which give physiologically acceptable salts.

For instance, the acid of the formula I may be converted with a base (e.g. sodium or potassium hydroxide or carbonate) to the corresponding metal salt, especially alkali metal or alkaline earth metal salt, or to the corresponding ammonium salt.

Suitable bases for this reaction include, in particular, organic bases which give physiologically acceptable salts, such as ethanolamine, for example,

Alternatively, a base of the formula I may be converted to the corresponding acid addition salt using an acid, for example by reacting equivalent amounts of the base

and the acid in an inert solvent such as ethanol, followed by evaporative concentration. Particularly suitable acids for this reaction are those which give physiologically acceptable salts. For instance, inorganic acids may be used, examples being sulfuric acid, nitric acid, hydrohalic acids such as hydrochloric acid or hydrobromic acid, phosphoric acids such as orthophosphoric acid, sulfamic acid, and also organic acids, especially aliphatic, alicyclic, araliphatic, aromatic or heterocyclic monobasic or polybasic carboxylic, sulfonic or sulfuric acids, examples being formic acid, acetic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methane- or ethane-sulfonic acid, ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, naphthalene-mono- and -disulfonic acids, and laurylsulfuric acid. Salts with physiologically unacceptable acids, e.g. picrates, may be used to isolate and/or purify the compounds of the formula I.

The invention additionally provides pharmaceutical preparations comprising at least one compound of the formula I and/or one of its physiologically acceptable salts and/or solvates for treating angina, high blood pressure, high pulmonary pressure, congestive heart failure, atherosclerosis, conditions of reduced circulation through the cardiac vessels, peripheral vascular diseases, stroke, bronchitis, allergic asthma, chronic asthma, allergic rhinitis, glaucoma, irritable bowel syndrome, tumours, renal insufficiency and cirrhosis of the liver and for treating female impotence.

These preparations may be used as medicaments in human or veterinary medicine. Suitable excipients include

organic or inorganic substances which are suitable for enteral (e.g. oral), parenteral or topical application and which do not react with the novel compounds, examples being water, vegetable oils, benzyl alcohols, alkylene glycols, polyethylene glycols, glycerol triacetate, gelatin, carbohydrates such as lactose or starch, magnesium stearate, talc, and petroleum jelly. For oral administration use is made in particular of tablets, pills, coated tablets, capsules, powders, granules, syrups, juices or drops; for rectal administration particular use is made of suppositories; for parenteral administration particular use is made of solutions, preferably oily or aqueous solutions, and also suspensions, emulsions or implants; for topical application, particular use is made of ointments, creams or powders. The novel compounds may also be lyophilized and the resulting lyophilizates used, for example to produce preparations for injection. The preparations indicated may be sterilized and/or may comprise auxiliaries such as lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing the osmotic pressure, buffer substances, colorants, flavourings and one or more further active substances, for example one or more vitamins.

The compounds of the formula I and their physiologically acceptable salts may be used in the control of diseases where an increase in the level of cGMP (cyclic guanosine monophosphate) leads to inhibition or prevention of inflammation and to muscle relaxation. Particular use may be made of the compounds of the invention in treating angina, high blood pressure, high pulmonary pressure, congestive heart failure, atherosclerosis, conditions of reduced circulation through the cardiac vessels, peripheral vascular diseases, stroke, bronchitis, allergic asthma, chronic asthma, allergic rhinitis, glaucoma, irritable bowel syndrome, tumours, renal insufficiency and

cirrhosis of the liver and for treating female impotence.

In these indications the substances are generally administered preferably in doses of between approximately 1 and 500 mg, in particular between 5 and 100 mg per dose unit. The daily dose is preferably between approximately 0.02 and 10 mg/kg of body weight. The specific dose for each patient depends, however, on a wide variety of factors, for example on the efficacy of the specific compound used, on age, body weight, general state of health, gender, on the diet, on the time and route of administration, on the excretion rate, medicament combination and severity of the particular disease to which the therapy is applied. Oral administration is preferred.

Above and below, all temperatures are stated in °C. In the examples below, "customary workup" means the following: water is added if necessary, the formulation is adjusted to a pH of between 2 and 10 if necessary, depending on the constitution of the end product, and is extracted with ethyl acetate or dichloromethane, the organic phase is separated off, dried over sodium sulfate and concentrated by evaporation, and the residue is purified by chromatography on silica gel and/or by crystallization.

Mass spectrometry (MS): EI (electronic impact ionization) M^+
FAB (fast atom bombardment) $(M+H)^+$

The invention provides in particular for the use of the compounds of the formula I set out in the examples below, and their physiologically acceptable salts and/or solvates, for preparing a medicament for treating angina, high blood pressure, high pulmonary pressure, congestive heart failure, atherosclerosis, conditions of reduced circulation through the cardiac vessels, peripheral vascular diseases, stroke,

bronchitis, allergic asthma, chronic asthma, allergic rhinitis, glaucoma, irritable bowel syndrome, tumours, renal insufficiency and cirrhosis of the liver and for treating female impotence.

Example 1

Methyl 3-(4-chlorobenzothieno[2,3-d]pyrimidin-2-yl)propionate [obtainable by cyclizing methyl 2-amino-5,6,7,8-tetrahydrobenzothiophene-3-carboxylate with methyl 3-cyanopropionate, dehydrogenating the product with sulfur and then chlorinating that product with phosphorus oxychloride/dimethylamine] and 3-chloro-4-methoxybenzylamine ("A") in N-methylpyrrolidone are stirred at 110° for 5 hours. The solvent is removed and the product is subjected to customary workup. This gives methyl 3-[4-(3-chloro-4-methoxybenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]propionate as a colourless oil.

Analogous reaction of "A"

with methyl 2-(4-chlorobenzothieno[2,3-d]pyrimidin-2-yl)acetate gives
methyl 2-[4-(3-chloro-4-methoxybenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]acetate.

Analogous reaction of 3,4-methylenedioxybenzylamine

with methyl 3-(4-chlorobenzothieno[2,3-d]pyrimidin-2-yl)propionate gives
methyl 3-[4-(3,4-methylenedioxybenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]propionate.

Analogous reaction of "A"

with methyl 4-(4-chlorobenzothieno[2,3-d]pyrimidin-2-yl)butyrate gives

methyl 4-[4-(3-chloro-4-methoxybenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]butyrate.

Analogous reaction of 3,4-methylenedioxybenzylamine

with methyl 4-(4-chlorobenzothieno[2,3-d]pyrimidin-2-yl)butyrate gives
methyl 4-[4-(3,4-methylenedioxybenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]butyrate.

Analogous reaction of "A"

with methyl 5-(4-chlorobenzothieno[2,3-d]pyrimidin-2-yl)valerate gives
methyl 5-[4-(3-chloro-4-methoxybenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]valerate.

Analogous reaction of 3,4-methylenedioxybenzylamine

with methyl 5-(4-chlorobenzothieno[2,3-d]pyrimidin-2-yl)valerate gives
methyl 5-[4-(3,4-methylenedioxybenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]valerate.

Analogous reaction of "A"

with methyl 7-(4-chlorobenzothieno[2,3-d]pyrimidin-2-yl)heptanoate gives
methyl 7-[4-(3-chloro-4-methoxybenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]heptanoate.

Analogous reaction of 3,4-methylenedioxybenzylamine

with methyl 7-(4-chlorobenzothieno[2,3-d]pyrimidin-2-yl)heptanoate gives
methyl 7-[4-(3,4-methylenedioxybenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]heptanoate.

Analogous reaction of "A"

with methyl 2-[4-(4-chlorobenzothieno[2,3-d]pyrimidin-2-yl)cyclohex-1-yl]acetate gives
methyl 2-{4-[4-(3-chloro-4-methoxybenzylamino)-benzothieno[2,3-d]pyrimidin-2-yl]cyclohexyl-1-yl}acetate.

Analogous reaction of 3,4-methylenedioxybenzylamine

with methyl 2-[4-(4-chlorobenzothieno[2,3-d]pyrimidin-2-yl)cyclohex-1-yl]acetate gives
methyl 2-{4-[4-(3,4-methylenedioxybenzylamino)-benzothieno[2,3-d]pyrimidin-2-yl]cyclohexyl-1-yl}acetate.

Analogous reaction of benzylamine

with methyl 3-(4-chlorobenzothieno[2,3-d]pyrimidin-2-yl)propionate gives
methyl 3-(4-benzylaminobenzothieno[2,3-d]-pyrimidin-2-yl)propionate;

with methyl 4-(4-chlorobenzothieno[2,3-d]pyrimidin-2-yl)butyrate gives
methyl 4-(4-benzylaminobenzothieno[2,3-d]-pyrimidin-2-yl)butyrate;

with methyl 5-(4-chlorobenzothieno[2,3-d]pyrimidin-2-yl)valerate gives
methyl 5-(4-benzylaminobenzothieno[2,3-d]-pyrimidin-2-yl)valerate.

Analogous reaction of "A"

with methyl 4-(4-chlorobenzothieno[2,3-d]pyrimidin-2-yl)cyclohexanecarboxylate gives
methyl 4-[4-(3-chloro-4-methoxybenzylamino)benzo-thieno[2,3-d]pyrimidin-2-yl]cyclohexanecarboxylate

and analogous reaction of 3,4-methylenedioxybenzylamine gives

methyl 4-[4-(3,4-methylenedioxybenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]cyclohexanecarboxylate.

Example 2

Methyl 3-[4-(3-chloro-4-methoxybenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]propionate is dissolved in ethylene glycol monomethyl ether and following addition of 32% NaOH the solution is stirred at 110° for 5 hours. Following the addition of 20% HCl it is extracted with dichloromethane. Addition of petroleum ether gives 3-[4-(3-chloro-4-methoxybenzylamino)-benzothieno[2,3-d]pyrimidin-2-yl]propionic acid, m.p. 218°.

The precipitated crystals are dissolved in isopropanol, and ethanolamine is added. Crystallization gives 3-[4-(3-chloro-4-methoxybenzylamino)benzothieno[2,3-d]-pyrimidin-2-yl]propionic acid, ethanolamine salt.

The following compounds are obtained analogously:

4-[4-(3-chloro-4-methoxybenzylamino)benzothieno-[2,3-d]pyrimidin-2-yl]butyric acid, m.p. 225°; ethanolamine salt m.p. 150°;

5-[4-(3-chloro-4-methoxybenzylamino)benzothieno-[2,3-d]pyrimidin-2-yl]valeric acid, m.p. 210°; ethanolamine salt m.p. 141°;

4-[4-(3,4-methylenedioxybenzylamino)benzothieno-[2,3-d]pyrimidin-2-yl]butyric acid, hydrochloride, m.p. 245°.

The carboxylic acids below are obtained analogously from the esters set out under Example 1:

2-[4-(3-chloro-4-methoxybenzylamino)benzothieno-[2,3-d]pyrimidin-2-yl]acetic acid,

3-[4-(3,4-methylenedioxybenzylamino)benzothieno-[2,3-d]pyrimidin-2-yl]propionic acid,

5-[4-(3,4-methylenedioxybenzylamino)benzothieno-[2,3-d]pyrimidin-2-yl]valeric acid,

7-[4-(3-chloro-4-methoxybenzylamino)benzothieno-[2,3-d]pyrimidin-2-yl]heptanoic acid,

7-[4-(3,4-methylenedioxybenzylamino)benzothieno-[2,3-d]pyrimidin-2-yl]heptanoic acid,

2-{4-[4-(3-chloro-4-methoxybenzylamino)-benzothieno[2,3-d]pyrimidin-2-yl]cyclohexyl-1-yl}acetic acid,

2-{4-[4-(3,4-methylenedioxybenzylamino)-benzothieno[2,3-d]pyrimidin-2-yl]cyclohexyl-1-yl}acetic acid,

3-(4-benzylaminobenzothieno[2,3-d]pyrimidin-2-yl)-propionic acid,

4-(4-benzylaminobenzothieno[2,3-d]pyrimidin-2-yl)-butyric acid,

5-(4-benzylaminobenzothieno[2,3-d]pyrimidin-2-yl)-valeric acid,

4-[4-(3-chloro-4-methoxybenzylamino)benzothieno-[2,3-d]pyrimidin-2-yl]cyclohexanecarboxylic acid, ethanolamine salt, m.p. 167°;

4-[4-(3,4-methylenedioxybenzylamino)benzothieno-[2,3-d]pyrimidin-2-yl]cyclohexanecarboxylic acid, ethanolamine salt, m.p. 143°.

Example 3

A mixture of 1.5 g of methyl 4-(4-chlorobenzothieno[2,3-d]pyrimidin-2-yl)phenylcarboxylate ("B"), prepared by dehydrogenating the corresponding 5,6,7,8-tetrahydrobenzothieno[2,3-d]pyrimidine compound with sulfur and chlorinating the product with phosphorus oxychloride/dimethylamine, and 1.5 g of 3-chloro-4-methoxybenzylamine in 20 ml of N-methylpyrrolidone is heated at 110° for 4 hours. After cooling, it is subjected to customary workup. This gives 2.6 g of methyl 4-[4-(3-chloro-4-methoxybenzylamino)[1]benzothieno[2,3-d]pyrimidin-2-yl]benzoate, m.p. 203-204°.

In analogy to Example 2, 1.2 g of the ester gives 1.0 g of

4-[4-(3-chloro-4-methoxybenzylamino)[1]-benzothieno[2,3-d]pyrimidin-2-yl]benzoic acid, ethanolamine salt, m.p. 189-190°.

In analogy to Example 1, "B" and 3,4-methylenedioxybenzylamine give methyl 4-[4-(3,4-methylenedioxybenzylamino)[1]benzothieno[2,3-d]pyrimidin-2-yl]-benzoate, whose ester hydrolysis gives 4-[4-(3,4-methylenedioxybenzylamino)[1]benzothieno[2,3-d]-pyrimidin-2-yl]benzoic acid, sodium salt, m.p. >260°.

Analogous reaction gives the compound

4-[4-(3-chloro-4-methoxybenzylamino)[1]-benzothieno[2,3-d]pyrimidin-2-yl]phenylacetic acid, ethanolamine salt, m.p. 130°;

and

4-[4-(3,4-methylenedioxybenzylamino)[1]-benzothieno[2,3-d]pyrimidin-2-yl]phenylacetic acid, ethanolamine salt, m.p. 202°.

Example 4

One equivalent of 3-[4-(3-chloro-4-methoxybenzylamino)-benzothieno[2,3-d]pyrimidin-2-yl]propionic acid and 1.2 equivalents of thionyl chloride are stirred in dichloromethane for 2 hours. The solvent is removed to give 3-[4-(3-chloro-4-methoxybenzylamino)benzothieno-[2,3-d]pyrimidin-2-yl]propionyl chloride.

This is transferred to aqueous ammonia, the mixture is stirred for an hour, and customary workup gives 3-[4-(3-chloro-4-methoxybenzylamino)benzothieno[2,3-d]-pyrimidin-2-yl]propionamide.

Example 5

One equivalent of DMF and 1 equivalent of oxalyl chloride are dissolved in acetonitrile at 0°. Thereafter, 1 equivalent of 3-[4-(3-chloro-4-methoxybenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]-propionamide is added. The mixture is subsequently stirred for an hour. Customary workup gives 3-[4-(3-chloro-4-methoxybenzylamino)benzothieno[2,3-d]-pyrimidin-2-yl]propionitrile.

Example 6

In analogy to Examples 1, 2 and 3, reaction of the corresponding chloropyrimidine derivatives with 3,4-ethylenedioxybenzylamine gives the following carboxylic acids:

4-[4-(3,4-ethylenedioxybenzylamino)benzothieno-[2,3-d]pyrimidin-2-yl]butyric acid,

3-[4-(3,4-ethylenedioxybenzylamino)benzothieno-[2,3-d]pyrimidin-2-yl]propionic acid,

5-[4-(3,4-ethylenedioxybenzylamino)benzothieno-[2,3-d]pyrimidin-2-yl]valeric acid,

7-[4-(3,4-ethylenedioxybenzylamino)benzothieno-[2,3-d]pyrimidin-2-yl]heptanoic acid,

2-{4-[4-(3,4-ethylenedioxybenzylamino)benzothieno-[2,3-d]pyrimidin-2-yl]cyclohexyl-1-yl}acetic acid,

4-[4-(3,4-ethylenedioxybenzylamino)benzothieno-[2,3-d]pyrimidin-2-yl]cyclohexanecarboxylic acid,

4-[4-(3,4-ethylenedioxybenzylamino) [1] benzothieno[2,3-d]pyrimidin-2-yl]benzoic acid, decomp. 220-230°;

4-[4-(3,4-ethylenedioxybenzylamino)[1]benzothieno-[2,3-d]pyrimidin-2-yl]benzoic acid, ethanolamine salt, m.p. 252°;

4-[4-(3,4-ethylenedioxybenzylamino)[1]benzothieno-[2,3-d]pyrimidin-2-yl]phenylacetic acid.

Analogous reaction with 3,4-dichlorobenzylamine gives the following compounds:

4-[4-(3,4-dichlorobenzylamino)benzothieno[2,3-d]-pyrimidin-2-yl]butyric acid,

3-[4-(3,4-dichlorobenzylamino)benzothieno[2,3-d]-pyrimidin-2-yl]propionic acid,

5-[4-(3,4-dichlorobenzylamino)benzothieno[2,3-d]-pyrimidin-2-yl]valeric acid, ethanolamine salt, m.p. 160°;

7-[4-(3,4-dichlorobenzylamino)benzothieno[2,3-d]-pyrimidin-2-yl]heptanoic acid,

2-{4-[4-(3,4-dichlorobenzylamino)benzothieno-[2,3-d]pyrimidin-2-yl]-cyclohexyl-1-yl acetic acid,

4-[4-(3,4-dichlorobenzylamino)benzothieno[2,3-d]-pyrimidin-2-yl]cyclohexanecarboxylic acid,

4-[4-(3,4-dichlorobenzylamino)[1]benzothieno-[2,3-d]pyrimidin-2-yl]benzoic acid,

4-[4-(3,4-dichlorobenzylamino)[1]benzothieno-[2,3-d]pyrimidin-2-yl]phenylacetic acid.

Analogous reaction with 3-chloro-4-ethoxybenzylamine gives the following compounds:

4-[4-(3-chloro-4-ethoxybenzylamino)benzothieno-[2,3-d]pyrimidin-2-yl]butyric acid,

3-[4-(3-chloro-4-ethoxybenzylamino)benzothieno-[2,3-d]pyrimidin-2-yl]propionic acid,

5-[4-(3-chloro-4-ethoxybenzylamino)benzothieno-[2,3-d]pyrimidin-2-yl]valeric acid,

7-[4-(3-chloro-4-ethoxybenzylamino)benzothieno-[2,3-d]pyrimidin-2-yl]heptanoic acid,

2-{4-[4-(3-chloro-4-ethoxybenzylamino)benzothieno-[2,3-d]pyrimidin-2-yl]-cyclohexyl-1-yl acetic acid,

4-[4-(3-chloro-4-ethoxybenzylamino)benzothieno-[2,3-d]pyrimidin-2-yl]cyclohexanecarboxylic acid,

4-[4-(3-chloro-4-ethoxybenzylamino)[1]benzothieno-[2,3-d]pyrimidin-2-yl]benzoic acid, m.p. 185-187°;

4-[4-(3-chloro-4-ethoxybenzylamino)[1]benzothieno-[2,3-d]pyrimidin-2-yl]phenylacetic acid.

Analogous reaction with 3-chloro-4-isopropoxybenzylamine gives the following compounds:

4-[4-(3-chloro-4-isopropoxybenzylamino)-benzothieno[2,3-d]pyrimidin-2-yl]butyric acid,

3-[4-(3-chloro-4-isopropoxybenzylamino)-benzothieno[2,3-d]pyrimidin-2-yl]propionic acid,

5-[4-(3-chloro-4-isopropoxybenzylamino)-benzothieno[2,3-d]pyrimidin-2-yl]valeric acid, ethanolamine salt, m.p. 130°;

7-[4-(3-chloro-4-isopropoxybenzylamino)-benzothieno[2,3-d]pyrimidin-2-yl]heptanoic acid,

2-{4-[4-(3-chloro-4-isopropoxybenzylamino)-benzothieno[2,3-d]pyrimidin-2-yl]-cyclohexy-1-yl acetic acid,

4-[4-(3-chloro-4-isopropoxybenzylamino)-benzothieno[2,3-d]pyrimidin-2-yl]cyclohexane-carboxylic acid,

4-[4-(3-chloro-4-isopropoxybenzylamino)[1]-benzothieno[2,3-d]pyrimidin-2-yl]benzoic acid, m.p. 240-241°;

4-[4-(3-chloro-4-isopropoxybenzylamino)[1]-benzothieno[2,3-d]pyrimidin-2-yl]phenylacetic acid.

The examples below relate to pharmaceutical preparations:

Example A: Injection vials

A solution of 100 g of an active substance of the formula I and 5 g of disodium hydrogen phosphate in 3 l of double-distilled water is adjusted to a pH of 6.5 using 2 N hydrochloric acid, subjected to sterile filtration, dispensed into injection vials, lyophilized under sterile conditions and aseptically sealed. Each injection vial contains 5 mg of active substance.

Example B: Suppositories

A mixture of 20 g of an active substance of the formula I is melted with 100 g of soya lecithin and 1400 g of cocoa butter, poured into moulds and allowed to cool. Each suppository contains 20 mg of active substance.

Example C: Solution

A solution is prepared from 1 g of an active substance of formula I, 9.38 g of $NaH_2PO_4 \cdot 2H_2O$, 28.48 g of $Na_2HPO_4 \cdot 12H_2O$ and 0.1 g of benzalkonium chloride in 940 ml of double-distilled water. The solution is adjusted to a pH of 6.8, made up to 1 l and sterilized by irradiation. This solution can be used in the form of eye drops.

Example D: Ointment

500 mg of an active substance of the formula I are mixed with 99.5 g of petroleum jelly under aseptic conditions.

Example E: Tablets

A mixture of 1 kg of active substance of the formula I, 4 kg of lactose, 1.2 kg of potato starch, 0.2 kg of talc and 0.1 kg of magnesium stearate is compressed in

a customary manner to tablets such that each tablet contains 10 mg of active substance.

Example F: Coated tablets

Tablets are pressed as in Example E and are subsequently coated in a customary manner with a coating of sucrose, potato starch, talc, tragacanth and colorant.

Example G: Capsules

2 kg of active substance of the formula I are filled in a customary manner into hard gelatin capsules, so that each capsule contains 20 mg of the active substance.

Example H: Ampoules

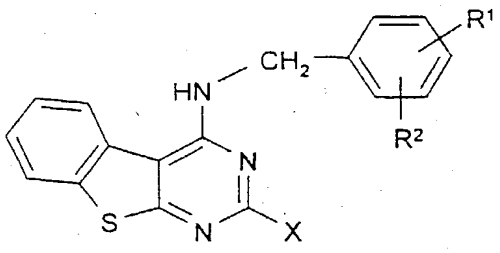
A solution of 1 kg of active substance of the formula I in 60 l of double-distilled water is subjected to sterile filtration, dispensed in ampoules, lyophilized under sterile conditions and aseptically sealed. Each ampoule contains 10 mg of active substance.

Example I: Inhalation spray

14 g of active substance of the formula I are dissolved in 10 l of isotonic NaCl solution and the solution is filled into commercially customary spray containers with a pump mechanism. The solution may be sprayed into the mouth or nose. One spray burst (approximately 0.1 ml) corresponds to a dose of approximately 0.14 mg.

Patent claims

1. Use of compounds of the formula I



I

in which

R^1, R^2 in each case independently of one another are H, A, OA, OH or Hal,

R^1 and R^2 together are also alkylene of 3-5 carbon atoms, $-O-CH_2-CH_2-$, $-CH_2-O-CH_2-$, $-O-CH_2-O-$ or $-O-CH_2-CH_2-O-$,

X is R^4, R^5 or R^6, monosubstituted by R^7,

R^4 is linear or branched alkylene of 1-10 carbon atoms, in which one or two CH_2 groups may have been replaced by -CH=CH- groups,

R^5 is cycloalkyl or cycloalkylalkylene of 5-12 carbon atoms,

R^6 is phenyl or phenylmethyl,

R^7 is COOH, COOA, $CONH_2$, CONHA, $CON(A)_2$ or CN,

A is alkyl of 1 to 6 carbon atoms and

Hal is F, Cl, Br or I

and their physiologically acceptable salts and/or solvates for preparing a medicament for treating angina, high blood pressure, high pulmonary pressure, congestive heart failure, atherosclerosis, conditions of reduced circulation through the cardiac vessels, peripheral vascular diseases, stroke, bronchitis, allergic asthma, chronic asthma, allergic rhinitis, glaucoma, irritable bowel syndrome, tumours, renal insufficiency and cirrhosis of the liver and for treating female impotence.

2. Use of compounds of the formula I according to Claim 1

(a) 3-[4-(3-chloro-4-methoxybenzylamino)benzo-[4,5]thieno[2,3-d]pyrimidin-2-yl]propionic acid;

(b) 4-[4-(3,4-methylenedioxybenzylamino)benzo-[4,5]thieno[2,3-d]pyrimidin-2-yl]butyric acid;

(c) 7-[4-(3,4-methylenedioxybenzylamino)benzo-[4,5]thieno[2,3-d]pyrimidin-2-yl]heptanoic acid;

(d) 7-[4-(3-chloro-4-methoxybenzylamino)benzo-[4,5]thieno[2,3-d]pyrimidin-2-yl]heptanoic acid;

(e) 5-[4-(3-chloro-4-methoxybenzylamino)benzo-[4,5]thieno[2,3-d]pyrimidin-2-yl]valeric acid;

(f) 2-{4-[4-(3-chloro-4-methoxybenzylamino)benzo-[4,5]thieno[2,3-d]pyrimidin-2-yl]-cyclohexyl-1-yl}acetic acid;

(g) 4-[4-(3,4-methylenedioxybenzylamino)benzo-[4,5]thieno[2,3-d]pyrimidin-2-yl]cyclohexane-carboxylic acid;

(h) 4-[4-(3,4-methylenedioxybenzylamino)benzo-[4,5]thieno[2,3-d]pyrimidin-2-yl]benzoic acid;

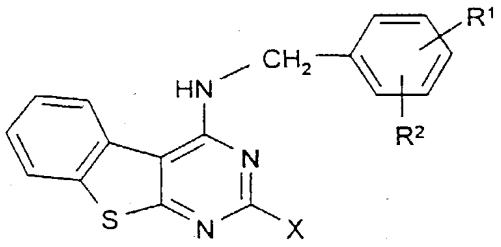
(i) 4-[4-(3,4-methylenedioxybenzylamino)benzo-[4,5]thieno[2,3-d]pyrimidin-2-yl]phenylacetic acid;

(k) 2-{4-[4-(3-chloro-4-methoxybenzylamino)benzo-[4,5]thieno[2,3-d]pyrimidin-2-yl]-cyclohexyl-1-yl }cyclohexanecarboxylic acid;

and their physiologically acceptable salts and/or solvates for preparing a medicament for treating angina, high blood pressure, high pulmonary pressure, congestive heart failure, atherosclerosis, conditions of reduced circulation through the cardiac vessels, peripheral vascular diseases, stroke, bronchitis, allergic asthma, chronic asthma, allergic rhinitis, glaucoma, irritable bowel syndrome, tumours, renal insufficiency and cirrhosis of the liver and for treating female impotence.

Abstract

Use of thienopyrimidines of the formula I



I

and their physiologically acceptable salts and/or solvates,

in which

R^1, R^2 and X are as defined in Claim 1,

to prepare a medicament for treating angina, high blood pressure, high pulmonary pressure, congestive heart failure, atherosclerosis, conditions of reduced circulation through the cardiac vessels, peripheral vascular diseases, stroke, bronchitis, allergic asthma, chronic asthma, allergic rhinitis, glaucoma, irritable bowel syndrome, tumours, renal insufficiency and cirrhosis of the liver and for treating female impotence.

Attorney Docket Number: MERCK 2397 #4

DECLARATION FOR PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

USE OF THIENOPYRIMIDINES

the specification of which

- ☐ is attached hereto
- ■ was filed on 24 AUGUST 2000 as United States Application Number or PCT International Application Number PCT/EP00/08258 and (if applicable) was amended on _____

I hereby authorize our attorneys to insert the serial number assigned to this application.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1.56.

I hereby claim foreign priority benefits under 35 U.S.C. §119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 USC §119			
APPLICATION NO.	COUNTRY	DAY/MONTH/YEAR FILED	PRIORITY CLAIMED
199 43 815.3	GERMANY	14 SEPTEMBER 1999	YES

I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below.

PROVISIONAL APPLICATION(S) UNDER 35 U.S.C. §119(e)	
APPLICATION NUMBER	FILING DATE

I hereby claim the benefit under 35 U.S.C. §120 of any United States application, or §365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. §112.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

PRIOR U.S./PCT INTERNATIONAL APPLICATION(S) DESIGNATED FOR BENEFIT UNDER 37 U.S.C. §120		
APPLICATION NO.	FILING DATE	STATUS — PATENTED, PENDING, ABANDONED

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected herewith: I. William Millen (19,544); John L. White (17,746); Anthony J. Zelano (27,969); Alan E.J. Branigan (20,565); John R. Moses (24,983); Harry B. Shubin (32,004); Brion P. Heaney (32,542); Richard J. Traverso (30,595); John A. Sopp (33,103); Richard M. Lebovitz (37,067); John H. Thomas (33,460); Catherine M. Joyce (40,668); Nancy J. Axelrod (44,014); James T. Moore (35,619); James E. Ruland (37,432); Jennifer J. Branigan (40,921) and Robert E. McCarthy (46,044)

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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☐ Additional joint inventors are named on separately numbered sheets attached hereto.